AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Group Art Unit 1632

In re

Patent Application of

Ralph R. Weichselbaum, et al.

Application No. 08/289,290

Confirmation No.: 1375

Filed: August 11, 1994

Examiner: Li, Qian J.

"CONSTITUTIVE GENE EXPRESSION IN CONJUNCTION WITH IONIZING RADIATION"

I, Anna Poppe, hereby certify that this correspondence is being deposited with the US Postal Service as first class mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450, on the date of my signature.

Anna Poppe
Signature

March 8, 2005
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Sir:

Transmitted herewith, in triplicate, is an Appellants' Reply to Examiner's Answer in the above-identified application.

No fee is believed due in connection with this submission. However, in the event Applicants have overlooked a requirement for payment of fees, please charge or credit Deposit Account No. 50-0842.

Respectfully submitted,

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APPELLANTS' REPLY TO EXAMINER'S ANSWER

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Alexandria, VA 22313-1450

Sir:

In the matter of the above-identified application, and in response to the Examiner's Answer mailed January 19, 2005, Appellants respectfully submit this Reply Brief for consideration by the Board.

STATUS OF CLAIMS AFTER EXAMINER'S ANSWER

A. Amendment after Final Rejection under 37 CFR 1.116 submitted March 1, 2005

The Examiner's Answer indicates at page 13 that an amendment to claim 40 submitted after final rejection on April 2, 2003 was not entered because further claims were also amended. The Examiner indicates that the amendment "would have been entered if only claim 40 were amended."

To reduce the number of issues on Appeal, Appellants' undersigned representative contacted the Examiner to inquire whether an amendment to claim 40, submitted under 37 CFR 1.116, would be entered. The Examiner agreed that such an amendment was proper and would be entered. Accordingly, an Amendment was filed on March 1, 2005. Based on the Examiner's representation, it is believed that this amendment will be entered and the outstanding rejection of claim 40 under 35 USC §112, first paragraph will be withdrawn by the Examiner.

B. Claims on Appeal

Claims 1-3, 6, 8-14, 18-22, 26-29 and 31-42 are pending in the application. Based on the above-noted Amendment after Final Rejection, it is believed that the claims now subject to this Appeal are 29 and 37. The remaining pending claims are believed to be allowable.

SUMMARY OF THE INVENTION AFTER EXAMINER'S ANSWER

The Examiner's Answer indicates that the summary of the invention with respect to claims 29 and 37 is correct. Accordingly, Appellants stand on the summary submitted in the Appeal Brief regarding these claims.

The Examiner's Answer indicates that the summary of the invention claimed in claim 40 is incorrect in the Appellants' Brief with respect to the dose of ionizing radiation.

As indicated above, Appellants' have submitted an amendment to claim 40 under 37 CFR 1.116. After entry of the amendment, the invention of claim 40 is a process of inhibiting growth of a tumor in a host comprising the steps of: a) injecting into the tumor a therapeutically effective amount of the pharmaceutical composition defined by claim 29; and b) administering to the host an effective dose of ionizing radiation, whereby the growth of the tumor is inhibited by expression of the nucleic acid encoding TNF-α and the administration of ionizing radiation, wherein the total dose of ionizing radiation is between 50 and 70 Gray.

ISSUES AFTER EXAMINER'S ANSWER

The Examiner has withdrawn the rejection of claims 29 and 37 under 35 USC § 102(e) as being anticipated by Connelly et al. (U.S. Patent No. 5,935,935).

The Examiner has also withdrawn the rejection of claims 29 and 37 under 35 USC §102(e) as being anticipated by Glorioso et al. (U.S. Patent No. 6,228,356).

For the reasons noted above, it is believed that the new matter rejection of claim 40 under 35 USC § 112, first paragraph will be withdrawn by the Examiner.

Therefore, the only issue remaining for consideration by the Board is whether the rejection of claims 29 and 37 under 35 USC § 103(a) as obvious over Zhang et al. (U.S. Patent No. 6,143,290) in view of Walther et al. (Anticancer Res. (1993)) should be reversed.

APPELLANT'S ARGUMENT IN VIEW OF EXAMINER'S ANSWER

The Examiner has taken the position that claims 29 and 37 are obvious over Zhang et al. in view of Walther et al. Appellants strongly urge the Board to find that that Examiner has failed to establish a *prima facie* case of obviousness.

Claim 29 is directed to a pharmaceutical composition comprising a genetic construct comprising a nucleic acid that encodes a TNF-□ operatively linked to a constitutive promoter dispersed in a pharmacologically acceptable carrier, wherein the genetic construct is packaged within an adenovirus particle. Claim 37 is directed to the composition of claim 29 wherein the adenovirus particle contains a deletion of the E1 region and/or the E3 region of the adenoviral genome.

According to the Examiner, Zhang et al. teaches an adenovirus construct comprising a nucleic acid that encodes p53, which may be packaged in virions, and which may lack an E1 or E3 region. (Examiner's Answer, page 7.) The Examiner also states that Zhang et al. teach the use of a strong constitutive promoter in such adenovirus-p53 constructs and also teach dispersion of such constructs in a pharmaceutically acceptable solution. (Examiner's Answer, page 7.) The Examiner recognizes, however, that Zhang et al. does not teach an adenoviral vector comprising a nucleic acid that encodes TNF-α. (Examiner's Answer, page 8, emphasis added.)

The Examiner nonetheless contends that this deficiency is remedied by 1) Walther et al.'s disclosure of a nucleic acid encoding TNF-α packaged in a recombinant retrovirus particle; and 2) Zhang et al.'s teaching regarding the need for developing strategies alternative to retroviral vectors. (Examiner's Answer, page 8.) The Examiner concludes that it would have been obvious to combine the constructs taught by Zhang et al. and Walther et al. to arrive at the claimed invention.

The initial burden rests with the Examiner to show that the references suggest the modification and/or combination of the references, and that there would have been a

reasonable expectation of success in doing so. It is well established that "both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicants' disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). In the instant case, the references neither suggest modifying or combining the disclosures, nor provide any expectation of success, despite the Examiner's argument to the contrary.

First, the cited references provide no suggestion to combine their respective disclosures. The construct described in Zhang et al. is an adenoviral vector + p53 (a growth suppressor) coding sequence. The construct described in Walther et al. is a retroviral vector + TNF-α (a cytokine) coding sequence. Nothing in either reference suggests the mixing and matching of these constructs that the Examiner has asserted is obvious.

Zhang et al. consider the problem of developing improved methods for delivery of the p53 tumor suppressor gene to cancer cells *in vivo*. (Col. 2, lines 53-56.) Although the bulk of the discussion pertains to delivery of p53, Zhang et al. also hypothesize that "other growth control-related genes for cancer gene therapy, such as the retinoblastoma gene, antisense oncogenes... and other growth control-related genes" could be packaged in adenovirus vectors for delivery to cancer cells. (Col. 3, lines 7-13) Absent from Zhang et al. is any mention of TNF-α, or for that matter any other cytokine, that exhibits anti-cancer effects by modulating the type and duration of the immune response against tumor cells. TNF-α is not a "growth control-related" polypeptide. Thus, there is no suggestion in Zhang et al. that the adenoviral vectors described therein would be appropriate for delivery of TNF-α.

The Examiner has attempted to characterize Zhang et al. as discussing the problems associated with retroviral vectors for gene therapy <u>in general</u>. To the contrary, all Zhang et al. can be said to fairly suggest is that retroviral vectors are problematic for the delivery of p53, or other growth control-related genes, to cells. Zhang et al. surely do not suggest to the skilled artisan that adenovirus should be used in place of retrovirus

for every conceivable therapeutic application of gene therapy using viral vectors. In fact, nothing on the record remotely suggests interchangeability of adenoviral vectors for retroviral vectors or that vector selection can be made without regard to the gene to be delivered.

Similarly, Walther et al., while disclosing delivery of TNF-α to cells via a retroviral vector, make no mention or suggestion that such a retroviral vector would be, or should be, interchangeable with other types of vectors, including adenoviral vectors. Thus, neither reference provides any motivation to combine or modify Walther et al. and/or Zhang et al.

Even if one were to assume, for the sake of argument, that the skilled artisan would somehow combine Zhang et al. and Walther et al. to fortuitously arrive at the claimed invention, the references do not offer any reasonable expectation of success in making such a combination. As is known by practitioners in the art, the choice of viral vector for any particular therapeutic application is dependent on a number of factors. For example, the skilled artisan must consider whether the polypeptide encoded by the vector construct is likely to interact with viral replication and/or packaging. Conversely, viral products may interfere with trafficking or therapeutic function of the polypeptide delivered to the cell. Another factor to be considered is whether the host immune response against the viral vector or encoded polypeptide will preclude therapeutic efficacy. The cited references provide no indication as to how to solve or circumvent these problems with respect to the claimed composition.

Thus, the skilled artisan, upon reading the disclosures of Zhang et al. and Walther et al. would not have been provided with any indication that substituting the retroviral vector of Walther et al. with the adenoviral vector of Zhang et. al. in a construct encoding TNF-α would successfully produce the pharmaceutical composition presently claimed in claims 29 and 37.

In summary, Zhang et al. and Walther et al. do not suggest the subject matter of the appealed claims. Nor do the references provide the skilled artisan with any reasonable expectation of success in the claimed combination. Thus, the Examiner has failed to establish a *prima facie* case of obviousness under 35 USC §103 regarding claims 29 and 37.

CONCLUSION

In light of the foregoing, appellants respectfully request that the Board reverse the outstanding obviousness rejection of claims 29 and 37.

Respectfully submitted,

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APPENDIX

Claims pending in Application Serial No. 08/289,290

1. A process of treating a human cancer patient comprising providing to a cancer cell in said patient a nucleic acid encoding a radiosensitizing polypeptide operatively linked to a constitutive promoter and contacting said cell with ionizing radiation, whereby the nucleic acid is expressed to produce the radiosensitizing polypeptide and the cancer is treated.

2. The process of claim 1, wherein the nucleic acid encodes a TNF-α.

3. The process of claim 18, wherein the radioprotecting factor is MnSOD, IL-1 or IL-2.

6. The process of claim 1, wherein the constitutive promoter is the immediate-early CMV enhancer/promoter, the RSV enhancer/promoter, the SV40 early promoter, the SV40 late enhancer/promoter, the MMSV LTR, the SFFV enhancer/promoter, the EBV origin of replication, the β-actin promoter or the Egr enhancer/promoter.

8 . The process of claim 1, wherein said nucleic acid is provided by transfection by liposomes, adenovirus or HSV-1.

9. The process of claim 8, wherein the liposome comprises DOTMA, DOTMA/DOPE, or DORIE.

10. The process of claim 8, wherein the transfection is by adenovirus infection.

11. The process of claim 8, wherein the transfection is by HSV-1 infection.

12. A process of sensitizing a cell to the effects of ionizing radiation comprising transfecting the cell with an adenovirus vector construct comprising a nucleic acid that encodes a cytokine, wherein said cytokine is synthesized in and secreted from said cell.

13. The process of claim 12, wherein the nucleic acid that encodes the cytokine is positioned under control of a promoter other than an adenovirus promoter.

14. The process of claim 13, wherein the promoter is the immediate-early CMV enhancer/promoter, the RSV enhancer/promoter, the SV40 early promoter, the SV40 late enhancer/promoter, the MMSV LTR, the SFFV enhancer/promoter, the EBV origin of replication, the β-actin promoter or the Egr enhancer/promoter.

18. A process of radioprotecting a cell from the effects of ionizing radiation comprising:

(a) obtaining a genetic construct comprising a nucleic acid encoding a cell radioprotecting factor operatively linked to a constitutive promoter; and (b)

transfecting a cell with the genetic construct;

whereby said radioprotecting factor is expressed and said cell is protected from said effects.

19. The process of claim 18, wherein the transfecting is by liposomes, adenovirus, or HSV-1.

20. (The process of claim 19, wherein the liposome comprises DOTMA, DOTMA/DOPE, or DORIE.

21. The process of claim 19, wherein the transfection is by adenovirus infection.

22. The process of claim 19, wherein the transfection is by HSV-1 infection.

26. A process of radioprotecting a cell from the effects of ionizing radiation comprising transfecting the cell with an adenovirus vector construct comprising a nucleic acid encoding a radioprotecting factor in a mammalian cell.

27. The process of claim 26, wherein the nucleic acid is positioned under control of a promoter other than an adenovirus promoter.

28. The process of claim 27, wherein the promoter is the immediate-early CMV enhancer/promoter, the RSV enhancer/promoter, the SV40 early promoter, the SV40 late enhancer/promoter, the MMSV LTR, the SFFVs enhancer/promoter, the EBV origin of replication, the β-actin promoter or the Egr enhancer/promoter.

29. A pharmaceutical composition comprising a genetic construct comprising a nucleic acid that encodes a TNF-α operatively linked to a constitutive promoter dispersed in a pharmacologically acceptable carrier, wherein the genetic construct is packaged within an adenovirus particle.

31. A method of expressing a radioprotecting or radiosensitizing factor in a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 29.

32. The method of claim 31, wherein the administering is by means of an intravenous injection of from 10^8 to 10^{11} virus particles.

33. The method of claim 31, wherein the mammal is a mouse.

34. The method of claim 31, wherein the mammal is a human.

35. A process of inhibiting growth of a tumor comprising the steps of:

(a) delivering to said tumor a therapeutically effective amount of a DNA molecule comprising a constitutive promoter operatively linked to a region encoding a polypeptide having the ability to inhibit growth of a tumor cell, which coding region further is operatively linked to a transcription terminating region, whereby said polypeptide is expressed; and

(b) exposing said cell to an effective dose of ionizing radiation, whereby the growth of said tumor is inhibited by said polypeptide and ionizing radiation.

36. A method of assessing the response of a cell to the constitutive production of radiosensitizing or radioprotecting factors following ionizing radiation comprising:

(a) growing the cell in culture;

(b) transfecting the cell with a genetic construct comprising a nucleic acid that encodes the cell radiosensitizing factor or radioprotecting factor operatively linked to a constitutive promoter, whereby said nucleic acid is expressed to produce the radiosensitizing factor or radioprotecting factor;

(c) exposing the cell to an effective dose of ionizing radiation; and

(d) assessing the response of the cell.

37. The pharmaceutical composition of claim 29, wherein the adenovirus particle contains a deletion of the E1 region and/or the E3 region of the adenoviral genome.

38. A process of inhibiting growth of a tumor in a host comprising the steps of:

(a) injecting into the tumor a therapeutically effective amount of the pharmaceutical composition of claim 29, and

(b) administering to the host an effective dose of ionizing radiation, whereby the growth of the tumor is inhibited by expression of the nucleic acid encoding a TNF-α and the administration of ionizing radiation.

39. The process of claim 38, wherein the amount of the pharmaceutical composition is between 10^8 and 10^{11} plaque forming units.

40. The process of claim 38, wherein the total dose of ionizing radiation is between 50 and 70 Gray.

41. The process of claim 35, wherein the polypeptide is a TNF-α.

42. The process of claim 12, wherein the cytokine is a TNF-α.